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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

PCT

406, 400

Global Intellectual Property

AstraZeneca
151 85 SÖDERTÄLJE

| CODE | DATE | NTD |
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| | | |

ANKOM 01 OCT 2004

GIPS Date of mailing
(day/month/year)

30-09-2004

Applicant's or agent's file reference
100709-1 WO

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IMPORTANT NOTIFICATION

International application No.
PCT/SE2003/000856

International filing date (day/month/year)
27-05-2003

Priority date (day/month/year)
30-05-2002

Applicant
AstraZeneca AB
et al

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the *PCT Applicant's Guide*.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see Also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY
(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

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|-------------------|------|------|
| CODE | DATE | NTD |
| | | |
| ANKOM 01 OCT 2004 | | GIPS |

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|---|---|--|
| Applicant's or agent's file reference 100709-1 WO | FOR FURTHER ACTION See Form PCT/IPEA/409 <input checked="" type="checkbox"/> International filing date (day/month/year) PCT/SE 2003/000856 27.05.2003 | DATA ENTERED <input checked="" type="checkbox"/> Priority date (day/month/year) 30.05.2002 |
| International Patent Classification (IPC) or national classification and IPC C07D 209/30, 403/12, 417/12, 413/12, A6131/405, 31/4178, 31/4196, 31/422, 31/4709, 31/427, A61P 11/06, 11/00, 29/00 | | |
| Applicant AstraZeneca AB et al | | |

| | | | | | | | | | | | | | | | | | |
|--|---|-------------------------------------|-------------------------------|--------------------------|---------------------|-------------------------------------|--|--------------------------|---------------------------------------|-------------------------------------|---|--------------------------|------------------------------------|--------------------------|--|--------------------------|--|
| <p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>5</u> sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> (<i>sent to the applicant and to the International Bureau</i>) a total of <u>1</u> sheets, as follows:</p> <p><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (<i>sent to the International Bureau only</i>) a total of (indicate type and number of electronic carrier(s)) containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p> <p>4. This report contains indications relating to the following items:</p> <table> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. I Basis of the report</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. II Priority</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. IV Lack of unity of invention</td> </tr> <tr> <td><input checked="" type="checkbox"/></td> <td>Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VI Certain documents cited</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VII Certain defects in the international application</td> </tr> <tr> <td><input type="checkbox"/></td> <td>Box No. VIII Certain observations on the international application</td> </tr> </table> | | <input checked="" type="checkbox"/> | Box No. I Basis of the report | <input type="checkbox"/> | Box No. II Priority | <input checked="" type="checkbox"/> | Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability | <input type="checkbox"/> | Box No. IV Lack of unity of invention | <input checked="" type="checkbox"/> | Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement | <input type="checkbox"/> | Box No. VI Certain documents cited | <input type="checkbox"/> | Box No. VII Certain defects in the international application | <input type="checkbox"/> | Box No. VIII Certain observations on the international application |
| <input checked="" type="checkbox"/> | Box No. I Basis of the report | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> | Box No. II Priority | | | | | | | | | | | | | | | | |
| <input checked="" type="checkbox"/> | Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> | Box No. IV Lack of unity of invention | | | | | | | | | | | | | | | | |
| <input checked="" type="checkbox"/> | Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> | Box No. VI Certain documents cited | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> | Box No. VII Certain defects in the international application | | | | | | | | | | | | | | | | |
| <input type="checkbox"/> | Box No. VIII Certain observations on the international application | | | | | | | | | | | | | | | | |

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|---|---|
| Date of submission of the demand 17.12.2003 | Date of completion of this report 23.09.2004 |
| Name and mailing address of the IPEA/SE Patent- och registreringsverket Box 5055 S-102 42 STOCKHOLM Facsimile No. +46 8 667 72 88 | Authorized officer Eva Johansson/EÖ Telephone No. +46 8 782 25 00 |

Form PCT/IPEA/409 (cover sheet) (January 2004)

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/000856

Box No. I Basis of the report

1. With regard to the language, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

This report is based on a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of:

- international search (under Rules 12.3 and 23.1(b))
 publication of the international application (under Rule 12.4)
 international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the elements of the international application, this report is based on (replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):

the international application as originally filed/furnished

the description:

pages 1-48 as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

the claims:

pages 49-52 as originally filed/furnished

pages* _____ as amended (together with any statement) under Article 19

pages* 53 received by this Authority on 27-07-2004

pages* _____ received by this Authority on _____

the drawings:

pages _____ as originally filed/furnished

pages* _____ received by this Authority on _____

pages* _____ received by this Authority on _____

a sequence listing and/or any related table(s) – see Supplemental Box Relating to Sequence Listing.

3. The amendments have resulted in the cancellation of:

the description, pages _____

the claims, Nos. _____

the drawings, sheets/figs _____

the sequence listing (specify): _____

any table(s) related to the sequence listing (specify): _____

4. This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

the description, pages _____

the claims, Nos. _____

the drawings, sheets/figs _____

the sequence listing (specify): _____

any table(s) related to the sequence listing (specify): _____

* If item 4 applies, some or all of those sheets may be marked "superseded."

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/000856

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

 the entire international application claims Nos. 7 and 8

because:

 the said international application, or the said claims Nos. 7 and 8
relate to the following subject matter which does not require an international preliminary examination (*specify*):

See PCT Rule 67.1.(iv).: Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

 the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____
are so unclear that no meaningful opinion could be formed (*specify*): the claims, or said claims Nos. _____ are so inadequately supported
by the description that no meaningful opinion could be formed. no international search report has been established for said claims Nos. _____ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

has not been furnished

does not comply with the standard

the computer readable form

has not been furnished

does not comply with the standard

 the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in the Annex C-bis of the Administrative Instructions. See Supplemental Box for further details.

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/000856

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

| | | |
|-------------------------------|------------------|-----|
| Novelty (N) | Claims 1-6, 9 | YES |
| | Claims _____ | NO |
| Inventive step (IS) | Claims 1-6, 9 | YES |
| | Claims _____ | NO |
| Industrial applicability (IA) | Claims 1-9 | YES |
| | Claims _____ | NO |

2. Citations and explanations (Rule 70.7)

New amended claims 8 and 9 have been filed 2004-07-27.
 The new claim 8 is the same as the earlier claim 8 and the structure formula in claim 9 has been corrected.

The earlier claim 10, which relates to an intermediate, is deleted. Claim 11 is deleted.

The following documents are cited in the search report:

The cited documents 1-12 assign to the earlier claim 10.

D1 STN International, File CAPLUS, CAPLUS accession no. 1977:535057, Document no. 87:135057 & JP,A2, 52039671

D2 STN International, File CAPLUS, CAPLUS accession no. 2001:338492, Document no. 134:353315 & WO, A1, 2001032621

D3 Tetrahedron Letters, Vol. 26, no. 15, 1985, page 1827-1830

D4 STN International, File CAPLUS, CAPLUS accession no. 1988:549279, Document no. 109:149279

D5 J. Org. Chem., Vol. 66, no. 7, 2001, page 2434-2441

D6 Tetrahedron Letters, Vol. 42, no. 6, 2001, page 1077-1080

D7 Tetrahedron Letters, Vol. 42, no. 31, 2001, page 5187-5189

D8 J. Org. Chem., Vol. 61, no. 5, 1996, page 1573-1577

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.

PCT/SE 2003/000856

Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of: Box V

D9 EP 530907

D10 WO 9516687

D11 WO 9419321

D12 EP 576347

D13 EP 1170594 A2

D14 GB 1356834 A

D15 STN International, File Chemcats, Chemcats acc. no.
2000:1027702

D16 STN International, File CAPLUS, CAPLUS acc. no.
1983:488557, doc. no. 99:88557

D1-D12 disclose compounds, which were earlier included in the scope of previous claim 10. The compounds are excluded from the claims.

The claimed invention relates to novel indole-derivatives as pharmaceutical compounds for treating respiratory disorders and a process for their preparation.

The cited documents D13-D16 represent the general state of the art.

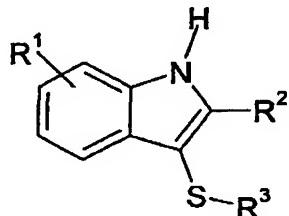
The invention defined in claims 1-6 and 9 is not disclosed by any of these documents.

The cited prior art does not give any indication that would lead a person skilled in the art to the claimed novel indole-derivatives as pharmaceutical compounds for treating respiratory disorders. Therefore, the claimed invention is not obvious to a person skilled in the art.

Accordingly, the invention defined in claims 1-6 and 9 is novel and is considered to involve an inventive step. The invention is industrially applicable.

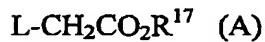
8. A method of treating according to claim 7 wherein the disease is asthma or rhinitis.

9. A process for the preparation of a compound of formula (I) which comprises reaction of a compound of formula (II):



(II)

10 in which R¹, R² and R³ are as defined in formula (I) or are protected derivatives thereof, with a compound of formula (A):



15 where R¹⁷ is an ester forming group and L is a leaving group in the presence of a base, and optionally thereafter in any order:

- removing any protecting group
- hydrolysing the ester group R¹⁷ to the corresponding acid
- forming a pharmaceutically acceptable salt.

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